Steps in immunosuppression for renal transplantation

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The technical feasibility of renal transplantation was established from the identical-twin experience in the 1950's [1]. The way in which these transplantations in the absence of an immunologic barrier contributed to the long and complex history of this field has been described in other reviews [2, 3]. The next and more difficult task was to develop techniques to prevent the rejection that followed transplantation when donors and recipients were not genetically identical.

Although total-body irradiation permitted occasional successes in the face of genetic disparity [4], the emergence of renal transplantation as a practical undertaking depended on the development of chemical immunosuppression. The first step toward this objective has often been overlooked, partly because its full significance was not perceived for more than a decade. In 1951, Billingham, Krohn, and Medawar [5] and Morgan [6] showed in rabbits that the rejection of primary skin grafts was significantly delayed by steroid therapy. Krohn [7] later proved that even second-set rejections in presensitized recipients could be favorably modified.

An equally important development was made possible by Hitchings and Elion [8, 9], who recognized the immunosuppressive properties of 6-mercaptopurine. Using this new drug, Schwartz and Dameshek [10, 11] demonstrated that rejection of rodent skin grafts could be mitigated. The work was promptly confirmed [12]. Calne [13] and other workers showed the same rejection-modifying effect after kidney transplantation in dogs, and within a year the 6-mercaptopurine derivative, azathioprine, became available for evaluation [9, 14].

It soon became obvious that the purine analogues were incompletely effective. Their true value was impossible to assess in the canine model, since optimal care of immunosuppressed recipients was not feasible in a kennel environment. Evolution of techniques of chemical immunosuppression to prevent or reverse rejection of whole organs was dependent upon observations after the technically simple procedure of renal transplantation in human recipients.

Double-drug regimens

The immunosuppressive protocols that have been developed with and for human renal transplantation are summarized in

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Table 1, exclusive of the historically important trials with total-body irradiation that were carried out in Boston in the late 1950's [4]. Because the first genuinely promising drug, azathioprine, proved to be effective only on rare occasions when given alone [15], the "modern" era was not entered until it was realized in 1962 and early 1963 that azathioprine and prednisone had an additive (or possibly synergistic) effect. With this drug combination, it was shown that rejection was a reversible process, and that the vigor of immunosuppression could often be lightened in some cases with the passage of time [16]. By the autumn of 1963, reports were published from four centers describing how azathioprine and prednisone could be used together [16–19]. It was of historical interest that Goodwin et al [20] had recognized at an earlier time and from an isolated observation that rejection might be a reversible process. Goodwin's patient was a young woman whose deteriorating graft function was temporarily improved when steroids were added to the base therapy with cyclophosphamide; the patient died of infection 144 days postoperatively.

At the outset, our policy was to begin therapy after renal transplantation with azathioprine, and to add high doses of prednisone with the first signs of rejection [16]. Because it was rare to escape rejection, even after transplantation from closely related donors, our recommendation soon became to begin treatment with both drugs immediately after transplantation, with a gradual subsequent reduction of the prednisone [21]. Such "double-drug therapy" has been the most commonly used immunosuppression throughout the world for almost 20 years.

The impetus given to clinical renal transplantation by double drug therapy was great. Although clinical kidney transplantation had been attempted sporadically between 1936 and 1962 (summarized by Groth [2]), the results had been so discouraging that most of these efforts had been discontinued. Early in 1963, there were less than ten clinical transplantation centers in the world, of which only five were active. With the advent of double drug therapy, new programs were started later in 1963 at the University of Minnesota (by William Kelly and Richard Lillehei), The Cleveland Clinic (by Wilhelm Kolff and Ralph Straffon), and in several other university centers. John Najarian, then working in San Francisco and subsequently in Minnesota, was one of the important new figures to enter into the field in the summer of 1964. The proliferation of centers then and later was overwhelming (Los Angeles has 13 certified centers). With these massive efforts, it did not take long to appreciate the limitations as well as the value of double drug therapy.

With transplantation from consanguineous donors under double drug treatment, chronic renal graft function became achiev-

Table 1. Immunosuppressive drug regimens and adjuncts for kidney transplantation

Agents	Year described and reported	Place	Deficiencies
Azathioprine	1962 [15]	Boston	Ineffective, dangerous
Azathioprine-steroids	1963 [16–19]	Denver, Richmond, Boston, Edinborough	Suboptimal
Thoracic duct drainage as adjunct	1963 [30]ᵃ	Stockholm	Nuisance: requires 20 to 30 days pretreatment
Thymectomy as adjunct	1963 [21, 35]	Denver	Unproven value
Splenectomy as adjunct	1963 [21, 35]	Denver	No longer necessary
ALG as adjunct	1966 [27]	Denver	Suboptimal
Cyclophosphamide substitute for azathioprine	1970 [29]	Denver	No advantage except for patients with azathioprine toxicity
Total lymphoid irradiation	1979 [33, 34]	Palo Alto, Minneapolis	Dangerous; extensive preparation; not quickly reversible
Cyclosporine alone	1978–1979 [44, 45]	Cambridge	Suboptimal
Cyclosporine-steroids	1980 [46, 47]	Denver	Under evaluation

ᵃ It was not realized until much later that pretreatment for 3 to 4 weeks before transplantation was a necessary condition [31].

able almost immediately in more than two thirds of the cases [21, 22]. However, during the first year after *cadaveric* renal transplantation, the graft loss was high, and in multicenter compilations it has been about 50%, even in recent times [23, 24]. With the increased and wiser use of dialysis for fall-back maintenance in the event of uncontrollable rejection, patient mortality has gone down [25]. But the morbidity of chronic immunosuppression (particularly with high-dose steroid therapy) has been well recognized, even after ostensibly "successful" operations [26]. The recognized need for better therapy prompted a number of deviations from the original formulas.

Triple-drug therapy and other modifications

Between 1963 and 1979, a number of modifications of, or additions to, the original double drug therapy were introduced (Table 1). The most promising approach was by lymphoid depletion with antilymphocyte globulin (ALG) [27]. Usually, the ALG was given intramuscularly or intravenously as a temporary supplement to azathioprine and prednisone during the first few weeks or months postoperatively. The greatest experience with this kind of treatment has been reported by Najarian et al [28]. More recently, ALG has had encouraging trials as an emergency agent, administered for the specific indication of a diagnosed rejection. "Triple-drug therapy" has been the second most commonly used immunosuppression. A theoretically important detail was the demonstration that cyclophosphamide could be freely substituted for azathioprine [29]. This was of interest because cyclophosphamide has been thought to selectively affect antibody-producing B cells. Because the results were not improved, the use of cyclophosphamide has been limited as a first line drug.

The results of 1-year graft survival after cadaveric renal transplantation under triple drug therapy (compared to that with azathioprine-prednisone) were improved in most but not all centers in which trials were conducted. After the discontinuance of ALG, there has been a moderately high rate of delayed rejection. The alternative of temporary lymphoid depletion with thoracic duct drainage (TDD) [30] in the preparation of patients for cadaveric renal transplantation [31] has proved to have the same disadvantage [32]. Lymphoid depletion by total lymphoid irradiation (TLI) for conditioning before grafting [33, 34] will

probably not be widely used in renal transplantation because of its inconvenience, and the difficulty of reversing its effects in the event of a complication from immunosuppression.

Two decades ago, thymectomy and splenectomy were introduced as adjuncts to drug therapy [21, 35]. Thymectomy did not have a demonstrable benefit and was abandoned, but a number of recent randomized trials have supported the value of splenectomy. Our opinion is that in the new era ushered in with cyclosporine (see later), splenectomy will no longer be needed.

Typing and transfusion

There was wide-spread discontent with all techniques of immunosuppression available from 1963 to 1978. Many kidney transplant surgeons attempted to provide a more advantageous biologic environment for the grafts by exploiting developments in tissue typing and matching, or by systematically conditioning prospective renal recipients with preoperative blood transfusions. The former efforts yielded disappointing results after cadaveric kidney transplantation [23, 24] probably because the genetic complexity of the histocompatibility system was too great to permit effective matching of nonrelated individuals. The latter practice of conditioning by transfusion has allowed an increased success rate in those patients not accidentally sensitized during their preparation [36]. The improved statistics with transfusion were explained in part by the weeding out from candidacy of those patients whose antibody responses disclosed them to be strong immune reactors. The consequence was the ability to treat a smaller number of recipients more successfully. However, for expansion of renal transplantation services, it was necessary to hope for better immunosuppressive drugs. This did not seem a realistic possibility until the advent of cyclosporine.

The cyclosporine era

The fungus extract cyclosporine was discovered and characterized biochemically by scientists at the Sandoz Corporation, Basel, Switzerland. Borel et al [37, 38] showed it to depress humoral and cellular immunity in mice, rats, and guinea pigs without the bone marrow depression which had frequently limited the doses of azathioprine and cyclophosphamide. Borel et al [37, 38] reported the unusual effectiveness of cyclosporine

Table 2. Cadaveric graft and patient survival in first cyclosporine trial, from December 1979 to September 1980

	At 6 mo	At 12 mo	At 18 mo	At 24 mo	At 25 to 36 mo
First grafts (57 in 57 patients)	48 (84.2%)	45 (79%)	44 (77.2%)	43 (75.4%)	39 (68.4%)
Retransplants (10 in 9 patients)	6 (60%)	6 (60%)	6 (60%)	6 (60%)	6 (60%)
Survival of the 66 patients	58 (87.9%)	57 (86.4%)	57 (86.4%)	56 (84.8%)	52 (78.8%)

in preventing or delaying rejection of mouse skin homografts, and analogous observations soon followed about the protection of a variety of whole organs in several animal species [39–43].

Cyclosporine was first used in 1978 in patients by Calne et al [44, 45]. That experience led to the recommendation that no other drug be routinely administered. When the drug became available to us in 1979, we soon realized that cyclosporine should be combined with steroid therapy from the outset [46, 47]. However, the steroid component with the latter new version of double drug therapy was much smaller than it was with azathioprine and prednisone. Although this was a learning experience with this drug combination, the 1-year kidney survival after primary cadaver transplantation was 79% [47] (Table 2).

The subsequent fate of grafts in these first-phase patients is summarized in Table 2. The 1- and 2-year primary graft survivals were 79 and 75.4% in a series of 57 cases. Of the 45 primary cadaveric recipients who still bore their functioning grafts at the end of a year, 39 (68.4% of the original 57) are still free of dialysis on their original transplants with followups of 2¼ to almost 3 years. Thirteen (22.8%) of the 57 recipients were switched to azathioprine from 4 months to 2 years after transplantation. Seven of the 13 grafts are still functioning. Rejection was common after the change [47].

In this pilot experience, 9 other patients underwent 10 cadaveric retransplantations after rejecting 1 to 3 previous grafts from months to years earlier under conventional immunosuppression. Six of the transplants were left at the end of the year, and all 6 are still functioning after 27 to 34 months (Table 2).

The patient mortality in these learning trials was too high (Table 2). Nine (13.6%) of these first 66 patients died in the first year, often of over-immunosuppression in futile and unwise efforts to retain badly rejecting kidneys or because of failure to distinguish the difference between nephrotoxicity and rejection [47]. During the second postoperative year, an additional patient with normal renal function died of a dissecting aortic aneurysm, giving a 2-year mortality of 10/66 (15.2%). During the third postoperative year, 4 more patients died, one with normal function who had a pulmonary embolus after a hip replacement. The other 3 died following return to chronic hemodialysis after their grafts were rejected. Cardiac complications caused 2 of these 3 deaths, and the third patient died of a perirectal abscess with a supralevator extension. Fifty-two (78.8%) of the original 66 patients are still living after 2 ¼ to 3 years, and 45 are dialysis free.

The first United States trials were at the University of Colorado [46, 47] and at the Peter Bent Brigham Hospital, Boston [48]. In the latter center, where cyclosporine was used alone and limited to the first 2 postoperative months, the results were disappointing [48]. Similar disillusionment was reported

by Sweny et al from London, combining cyclosporine with cytotoxic drugs [49]. Subsequent trials in Houston [50], Minneapolis [51], and at a later period in the Boston experience (unpublished) have verified the value of the cyclosporine-steroid combination. Calne et al [52], using steroids for the specific indication of rejection, have reported 85% 1-year cadaveric graft survival, and results about 10% below this have been obtained with the same approach in a collaborative European center trial [53].

The value of experience with cyclosporine-steroid therapy was evident in our second wave trials of cadaveric transplantation begun in March 1981. During 1981, 38 more patients received primary cadaveric homografts under treatment with cyclosporine and steroids. With a minimum followup of 11 to 20 months, 35 (92.1%) of these 38 patients still have adequately functioning first grafts (Table 3). During the same period, 32 other patients were treated with conventional azathioprine-prednisone management, the majority of whom were participants in a randomized control trial. The 1-year graft survival in the conventional group was 15/32 (49.9%). The divergence in results (Table 3) was so great that the randomized trial had to be discontinued.

Of great interest was a further series of 30 cadaveric *retransplantations* in 29 patients carried out in 1981, for which followups of almost 1 year to 1 ¾ years are available (Table 3). The 1-year graft survival was 76.6% in spite of the inclusion of 8 recipients whose preoperative sera had widely reacting T-warm antibodies. Twenty (69%) of these 29 recipients still are dialysis-free. A randomized control trial was not carried out because of the historically poor performance of retransplanted kidneys [54, 55], but the results (Table 3) have been more than twice as good as those achieved at this same institution (University of Pittsburgh) during the preceding 3 years. The good results achievable with retransplantation have added an extra incentive to avoid over-immunosuppression with the first kidney if there are unusual difficulties with rejection, since now there is such an excellent prognosis for a second effort.

The 1-year mortality in the 1981 Pittsburgh cadaveric series (all cyclosporine cases plus conventional therapy) was 2 in 99 (2%). The first death of a cyclosporine-treated patient was from a myocardial infarction 2 weeks after transplantation; he had a functioning kidney. The second death was of a patient who had rejected a kidney under azathioprine-steroid therapy. She died after 9 ½ months postoperatively, 3 months after returning to chronic hemodialysis. An additional cyclosporine-treated patient with good renal function died 1 ½ years after retransplantation of a ruptured abdominal aneurysm.

The incidence of lymphoma in the cyclosporine trials has been watched with interest. A total of 136 recipients were given primary or secondary cadaveric renal grafts in 1980 and in 1981. Two (1.5%) developed lymphomas with features which have

Table 3. Cadaveric graft and patient survival in second cyclosporine (and control) trial (1981)

	At 3 mo	At 6 mo	At 9 mo	At 11 mo	At 11 to 21 mo
Primary grafts with cyclosporine-steroids (N = 38)	36 (94.7%)	35 (92.1%)	35 (92.1%)	35 (92.1%)	35 (92.1%)
Primary grafts with azathioprine-steroids (N = 32)	22 (68.8%)	17 (53.1%)	16 (50%)	15 (46.9%)	14 (43.8%)
Retransplants with cyclosporine-steroids (N = 29 patients)	24 (80%)	23 (76.6%)	23 (76.6%)	23 (76.6%)	20 (66.7%)[b]
Survival in all 99 patients[a]	98	98	98	97	96 (97%)

[a] Two deaths after 2 weeks and 18 months were with functioning grafts (one each in the cyclosporine and retransplantation series) and were caused by myocardial infarction and ruptured abdominal aneurysm. The third patient (azathioprine series) was anephnic and died of gastrointestinal hemorrhage 9½ months after transplantation.

[b] Two of the 3 late graft losses were from chronic rejection after 12 and 13 months; the third was from death (ruptured aneurysm) after 18 months.

been described elsewhere [47, 56]. One of the lymphomas was an incidental autopsy finding in a patient who died of *Pneumocystis carinii* pneumonitis, and the other caused a small bowel perforation which was treated with resection. The latter patient is well 14 months later. A third patient with a perforated small bowel had a lymphoproliferative mass which was not thought to be a lymphoma [47]. She is well 2 ½ years after intestinal resection. Thus, there have been no deaths attributable to lymphoma. There have been no examples of *de novo* epithelial tumors.

Future prospects

It has become clear that cyclosporine will make possible the expansion of renal transplantation with a greater emphasis on the use of cadaveric donors than in the past. The results described above from our cyclosporine experience in 1980 and 1981 were obtained with random or nearly random donor-recipient matching, and for the most part without systematic preoperative recipient transfusion. The early behavior and later durability of these cadaveric kidneys has suggested that tissue matching will play a less prominent role in future transplantation practices than was envisioned in the past. It is likely that the systematic preoperative preparation of recipients with blood transfusions will be less widely practiced, since the potential hazards of recipient sensitization and antibody formation may be unnecessary penalties. With the ability to use smaller doses of steroids, the pool of acceptable recipients is apt to expand and to include more diabetics, older patients, and others who are currently considered to be at high risk. It is noteworthy that 17 of the patients included in the 1980 and 1981 experience (10 cyclosporine, 7 azathioprine) had type 1 diabetes; in this group there have been no deaths and 16 of the 17 are now dialysis-free. The cardiovascular complications which were responsible for most of the deaths after 1 year further reflected the fact that many high-risk patients were already being included in these trials. The good rate of success both with primary and secondary cadaveric transplantation will be an inducement to minimize the use of living related donors, and this latter practice will undoubtedly become increasingly obsolete.

As new teams begin using cyclosporine it will be important to avoid the unrealistic expectations about early convalescence that could be engendered by the high success rates that have already been achieved after cadaveric renal transplantations. In

a recent analysis of 42 consecutive cadaveric renal recipients treated by us [56], only a third had a completely uneventful recovery. Of the remainder, most developed rejection, which usually could be reversed readily with augmented steroid therapy. In every case, the differential diagnosis that required evaluation was rejection versus nephrotoxicity from cyclosporine. Fortunately, the complication of nephrotoxicity usually has promptly reversed with the reduction of cyclosporine doses, and as a last resort a change from cyclosporine to azathioprine can be made, but at a significant risk of subsequent rejection [57].

Most of the other side effects of cyclosporine have not been serious, including gum hyperplasia, tremor, regional flushing, or vague abdominal discomfort just after drug ingestion, and the development of breast fibroadenomas in women. Hepatotoxicity has been seen in about one fifth of the patients [46, 58], but this rarely has been serious enough in renal recipients to necessitate a change to azathioprine.

Lymphomas can be expected to develop with cyclosporine, just as has been documented with other forms of immunosuppression [59, 60]. However, the actual incidence may not be greater than it was with past forms of immunosuppression. The most accurate way of assessing the risk of lymphomas would be per month of immunosuppression, a kind of computation which would take into account the greater success rate with cyclosporine-steroids and the resulting need for continuing therapy. The conclusion that epithelial tumors will be less common than they are with conventional immunosuppression must be considered tentative, but the freedom to date from the epithelial tumors, which under conventional immunosuppression account for about three fourths of the *de novo* neoplasms [60], has been noteworthy to date. As experience with cyclosporine has accumulated worldwide, the specter of this drug being a spectacular tumor-producer has receded.

Acknowledgments

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